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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/764,163	01/16/2001	Robert F. Balint	PARE.002.02US	7613

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EXAMINER

GROSS, CHRISTOPHER M

ART UNIT	PAPER NUMBER
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1639

DATE MAILED: 12/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/764,163	BALINT ET AL.	
	Examiner	Art Unit	
	Christopher M. Gross	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 17 August 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 80 and 84-88 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 80, 84-88 is/are rejected.
- 7) ☒ Claim(s) 84 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Responsive to communications entered 8/17/2006. Claims 80 and 84-88 are pending. Claims 80 and 84-88 are under consideration.

In view of issues not raised previously in the prosecution history, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, applicant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

Priority

This application is a CIP of application 09/526106 filed 3/15/2000 (now ABN) and also claims benefit to provisional application 60/175968 filed 1/13/2000.

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Withdrawn Claim Rejections

Applicant's amendments to the claims have been considered and are hereby entered.

The rejections of claims 80, 84-88 under 35 USC 112, second paragraph set forth in the previous office action has been withdrawn in view of the amendments to the claims.

Maintained Provisional Claim Rejection: Double Patenting

In view of the new grounds of rejection below, claims 80, 84-88 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 63-74 of copending Application No. 10/668,778.

New Claim Objections

Claim 84 is objected to because of the following informalities: break point is spelled out as two words twice in line 2 whereas the antecedent breakpoint(s) found in claim 80 is spelled out as one word. Appropriate correction is required.

New Claim Rejections - 35 USC § 112

The following is a quotation of the **first** paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 80 and 84-88 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

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reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

The invention is broadly drawn to a circularly permuted beta-lactamase protein where the first interactor domain is fused to the circularly permuted beta-lactamase protein through the N-terminal breakpoint of the circularly permuted beta-lactamase protein and a and the second interactor domain is fused to the circularly permuted beta-lactamase protein through the C-terminal breakpoint.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, reduction to drawings, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a

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combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly* 119 F.3d at 1568. 43 USPQ2d at 1406.

Commensurate with Page 11 of the specification which states, "The methods detect the interaction of a first known or unknown interactor domain with a second unknown interactor domain...by bringing into close proximity members of a fragment pair of a marker protein or a circular permutation of a marker protein, such that the parent marker protein is reassembled to its original functionality," therein the interactor domains are taken as including species which interact with *known* as well as *unknown* ligands.

The specification does not describe a representative number of species in the genera of unknown interactor domains which work to provide a functionally reconstituted circularly permuted beta-lactamase protein upon binding of a first interactor domain and said second interactor domain to a single ligand. The skilled artisan cannot immediately envision what kinds of unknown interactor domains are truly capable of refolding beta-lactamase and therefore be included as part of the claimed genus.

Applicant has not provided functional characteristics coupled with a known or disclosed correlation between function and structure for known interactor domains which are compatible with the claimed invention. For example, a single amino acid such as tryptophan could be considered a small interactor domain, since it 'interacts' with tryptophan synthetase, yet it is not immediately obvious how one residue would be able to reconstitute beta-lactamase.

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Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the technique.

Therefore, only known interactor domains including the scFv antibody, fos/jun monomers and CD40, as set forth in example 11b, meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 80,85-86,88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for circularly permuted beta-lactamase comprising N and C interactor domains with a breakpoint between Glu197 and Leu198 it, does not reasonably provide enablement for the other breakpoints set forth in claims 85 and 86. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether undue experiment is necessitated.

These factors can include, but are not limited to:

- (1) the breadth of the claims;
- (2) the nature of the invention;
- (3) the state of the prior art;
- (4) the relative skill of those in the art;
- (5) the level of predictability in the art;
- (6) the amount of direction provided by the inventor;
- (7) the existence of working examples; and
- (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1 and 2) The breadth of the claims and the nature of the invention: The invention is broadly drawn to a circularly permuted beta-lactamase protein where the first interactor domain is fused to the circularly permuted beta-lactamase protein through the N-terminal breakpoint of the circularly permuted beta-lactamase protein and a and the second interactor domain is fused to the circularly permuted beta-lactamase protein through the C-terminal breakpoint.

(3 and 5) The state of the prior art and the level of predictability in the art:

Circularly permuted proteins have been studied in the art for some time. However, the impact of breaking the polypeptide chain and therein introducing a new positive (N) and negative (C) charge elsewhere in the tertiary structure of a protein is not yet predictable in the art, as noted by Pieper et al (1997 Biochemistry 36:8767 – IDS entry 5/5/2004) on page 8768 second paragraph.

Pieper et al, further point out on page 8770, under 'Design of the circularly permuted proteins' that beta-lactamase with a breakpoint at residue 211 (in the range set forth in claim 85 and 86) exhibited poor expression. Pieper et al also point out in the abstract that an analog with a breakpoint at residue 228 (as set forth in claims 85-86), while expressing well, showed a large decrease in catalytic activity as compared to the wild-type enzyme.

(4) The level of one or ordinary skill: The level of skill would be high, most likely at the Ph.D. level or equivalent number of years experience. However, such persons of ordinary skill in this art, *given its unpredictability*, would have to

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engage in undue (non-routine) experimentation to carry out the invention as claimed.

(6 and 7) The amount of direction provided by the inventor and the existence of working examples:

Example 11b of the specification demonstrates the claimed invention with a working example of beta-lactamase bearing a breakpoint between Glu197 and Leu198 and known interactor domains including CD40, a scFv antibody and fos/jun domains.

Example 11b is not generalizable toward other breakpoints because, as demonstrated by Pieper, different breakpoints have different consequences on making and using circularly permuted beta-lactamase.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The amount of experimentation necessary make and use the invention is substantial because the disclosed specification does not provide adequate protocols with regard which breakpoints would provide a circularly permuted beta-lactamase protein which may be functionally reconstituted only upon binding of said first interactor domain and said second interactor domain to a single ligand.

New Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 80 and 84 are rejected under 35 U.S.C. 102(b) as being anticipated by Pieper et al (1997 Biochemistry 36:8767 – IDS entry 5/5/2004).

Claims 80-88 were originally rejected (see Office Action mailed 5/5/2004 pp 9-10) on the basis that Pieper et al teach a circularly permuted beta-lactamase reading the claimed polypeptide.

The claimed invention is drawn to a polypeptide consisting essentially of: a first and second interactor domain and a circularly permuted beta-lactamase protein where the first interactor domain is fused to the circularly permuted beta-lactamase protein through the N-terminal breakpoint of the circularly permuted beta-lactamase protein and a and the second interactor domain is fused to the circularly permuted beta-lactamase protein through the C-terminal breakpoint of the circularly permuted beta-lactamase protein, wherein said circularly permuted beta-lactamase protein is functionally reconstituted only upon binding of said first interactor domain and said second interactor domain to a single ligand.

Claim 84 adds the limitation that said N-terminal breakpoint and C-terminal breakpoint are within a solvent exposed loop between elements of secondary structure within the beta-lactamase protein.

Applicant argued (see Applicant's arguments entered 10/13/2004 p18) that Pieper et al do not teach all elements and in particular that Pieper et al do

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not teach a first and second interactor domain fused to the N and C terminus of the circularly permuted beta-lactamase protein.

Applicant's arguments have been reconsidered and are they are not persuasive for the following reasons.

Pieper et al teach, throughout the document and especially the abstract a circularly permuted beta-lactamase which is joined at the native N and C termini, residues 31 and 290, respectively, through an eight residue linker peptide and new N and C termini are established between Gly253 and Lys254 (cp254) or Ala227 and Gly228 (cp228).

The topological changes (circular permutation) plus the insertion of said linker peptide according to Pieper et al would provide N and C termini peptide segments, which in of themselves are considered to represent *unknown* interactor domains. For example, the C and N terminal sequences represent unknown ligands (interactors) for an antibody raised against their primary sequence.

Commensurate with page 11 of the specification which states, "the methods detect interaction of a first known or unknown interactor domain with a second unknown interactor domain...", the new N and C termini of Pieper read on unknown interactor domains, such as set forth in claim 80.

Pieper et al teach on page 8768, third paragraph that the analog cp254 has a breakpoint in a loop distant from the beta-sandwich interface, which absent evidence to the contrary is solvent exposed, as set forth in claim 84.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Gross whose telephone number is (571)272-4446. The examiner can normally be reached on M-F 9-5:30.

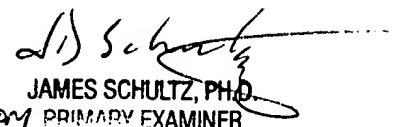
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz can be reached on 571 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christopher M Gross
Examiner
Art Unit 1639

cg


MARK L. SHIBUYA
PRIMARY EXAMINER


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